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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/705,022	UMLAUF, SCOTT	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *26-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *24 October 2002* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1-25 are pending examination.

Applicant's traversal, amendment to claims 1-25 in paper no. 13 is acknowledged and considered.

This application contains claim 26-41 drawn to an invention non-elected without traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

The corrected or substitute drawings were received on 10/24/02. These drawings are not acceptable because a fax copy of the drawings cannot be accepted by the Office (Applicant's attention is directed to MPEP 502.01). If the reply to the Final Rejection does not have a response to the 948, the response will be considered non-responsive. See 37 CFR 1.85(a).

Specification

The objection to the specification is moot in view of the clarification provided by the applicant.

However, the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See page 18). Applicant is required to delete the embedded hyperlink and/or any other form of browser-executable codes. Applicant's attention is directed to MPEP § 608.01.

The rejection for claims 1-25 under 112 written description and enablement is moot in view of applicants' traversal.

The rejection for claims 1-3, 9, 11, 14, and 20 under 112 second paragraph in moot in view of applicants' traversal.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 1-3, 11, and 14-15 are rejected under 35 U.S.C 103(a) as being unpatentable over Krieg et al. (US Patent No. 6,339,068) taken with Ellis et al. (IDS, Journal of Immunology, Vol. 56, 1996) in further view of either Zhang (IDS, Gene, 1996) or Li et al. (Human Immunology, Vol. 61, pp. 486-498, May 2000). Krieg teaches an immunostimulatory nucleic acid comprising at least one CpG-S motif and a nucleic acid encoding an antigen, wherein the nucleic acid further

comprises regulatory sequence for expression of DNA in eukaryotic cells and a method of using the nucleic acid to elicit an immune response in a mammalian subject (column 93-95, claims 1, 17, 18, 24, 25, and 30). Furthermore, Krieg teaches using a cell specific promoter that is operative in antigen-presenting cells (claim 25). In addition, the use of a pharmaceutically composition can be inferred, as it would otherwise be impossible to deliver the polynucleotide sequence to a subject. However, Krieg did not specifically teach that antigen presenting cell specific promoter is a co-stimulatory promoter obtained from a CD80 or CD86 gene.

However, at the time the invention was made, Ellis teaches that CD80 and CD86 genes are expressed only in antigen presenting cells (APCs) (abstract). Li teaches that the characterization of 5'-regulatory region (promoter region) of the human CD86 gene, which is expressed only in APCs (abstract and page 487). Zhang teaches that the CD80 promoter is expressed only in APCs (abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to have employ either the CD80 or CD86 promoter as the APC promoter in the method of Krieg. One of ordinary skill in the art would have been motivated to use the CD80 or CD86 promoter as the APC specific promoter in the construct of Krieg to elicit an immune response in vertebrate subjects because the CD80 and CD86 genes were known to one of ordinary skill in the art to express in antigen presenting cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant traverses the 103 rejection for the following reasons: The office has identified discrete elements of applicants recited combination and magically combine these elements

without finding the teaching or suggestion to have done so in the prior art. The motivation suggest by the office is clearly insufficient to establish a prima facie since it is the references that must suggest the desirability of making the combination, and not the applicants' specification. If knowledge of the claimed promoters was really a suitable motivation as the Office would argue, why then did Krieg not teach or suggest that CD 80 or CD86 promoters could be or should be used in the their constructs. If the office is correct in its assertion that there was a proper motivation to produce the claimed invention merely based on the basis that the promoters were known, and a field of skilled artisan somehow neglected to make this simple combination over the course of 3-4 years, then the office has actually identified a long-felt need in the art that was not met until applicants taught this combination. See pages 10-12.

Applicant's traversal is acknowledged and is not found persuasive. In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The totality of the prior at the time the application was made teaches a product for use in a method of stimulating comprising a nucleic acid sequence operatively linked to a promoter and using a cell-specific promoter that is operative in antigen-presenting cells (see Krieg). The only component not taught by Krieg is using either the CD 80 or 86 promoter, which are taught by Li or Zhang. Li teaches that the characterization of 5'-regulatory region (promoter region) of the human CD86 gene, which is expressed only in APCs. Zhang teaches that the CD80 promoter is expressed only in APCs. One of ordinary skill in the art would have been motivated to use the CD80 or CD86 promoter as

the APC specific promoter in the construct of Krieg to elicit an immune response in vertebrate subjects because the CD80 and CD86 genes were known to one of ordinary skill in the art to specifically express in antigen presenting cells.

Furthermore, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, the examiner has taken only knowledge, which was within the level of ordinary skill at the time the claimed invention was made.

Thus, the traversal is not found persuasive for the reasons set forth above and the rejection for claims 1-3, 11, and 14-15 remain under 103.

Claims 1-5 and 11-19 are rejected under 35 U.S.C 103(a) as being patentable over Krieg et al., Ellis et al., and either Zhang or Li Kuby taken with any of Gurunathan (IDS, AR-2), Pulendran (IDS, AS-2), or Wong (IDS, AP-2).

The rejections of the base claims 1 and 14 under 35 U.S.C. 103(a) are applied here as indicated above, e.g., Krieg taken with Ellis in further view of either Li or Zhang. However, Krieg taken with Ellis in further view of either Li or Zhang do not specifically teach that the APC specific promoter is obtained from a co-stimulatory promoter obtained from CD80 or CD86 for use in a method taught by Krieg in combination with at least one cytokine selected from the

group consisting of CD40L, TRANCE, or Flt-3L and administering the composition to elicit an immune response. In addition, Krieg taken with Ellis in further view of either Li or Zhang do not specifically teach that the APC specific promoter is obtained from a co-stimulatory promoter obtained from CD80 or CD86 further comprising a nucleotide sequence encoding at least one cytokine selected from the group consisting of CD40L, TRANCE, or Flt-3 a method taught by Krieg.

However, at the time the invention was made, Gurunathan reports that CD40 ligand has a central role in the induction of both humoral and cellular immunity (abstract). In addition, Gurunathan reports that the ability of CD40L DNA to enhance a broad array of immune responses makes it a potent adjuvant for diseases requiring humoral and/or cellular immunity (pg. 4570). Pulendran shows that administration of Flt-3 ligand, a cytokine capable of inducing large numbers of dendritic cells in vivo, (a) dramatically enhances the sensitivity of antigen-specific B and T cell responses to systemic injection of a soluble protein; (b) influences the class of antibody produced; and (c) enables productive immune responses to otherwise tolerogenic protocols (abstract). Wong reports that TRANCE enhances immune system cells by promoting the life span of mature dendritic cells (pg. 2078).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to combine the work of Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran, and Wong to produce an immunogenic composition comprising either a CD80 or CD86 promoter operably linked to a polynucleotide sequence encoding at least one antigen; and using at least one cytokine selected from the group consisting of CD40L, TRANCE, and Flt-3L to elicit an immune response in a vertebrate subject. One of ordinary skill

in the art would have been motivated to combine the immunogenic composition of Krieg, Ellis Li or Zhang taken with any of Gurunathan, Pulendran and Wong to enhance eliciting an immune response in subjects by assisting in regulating the development of immune effector cells (e.g. dendritic cells) as taught by Gurunathan, Pulendran and Wong.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to combine the work of Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong to produce an immunogenic composition comprising either a CD80 or CD86 promoter operably linked to a polynucleotide sequence encoding at least one antigen; and one polynucleotide sequence encoding at least one cytokine selected from the group consisting of CD40L, TRANCE, and Flt-3L to elicit an immune response in a vertebrate subject. One of ordinary skill in the art would have been motivated to combine the immunogenic composition of Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong to produce the polynucleotide sequence described above, for enhancing an immune response in subjects by assisting in regulating the development of immune effector cells (e.g. dendritic cells) as taught by Gurunathan, Pulendran and Wong.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant traverses the 103 rejection for the following reasons set forth above and: The office initial 4-way combination clearly fails to teach or suggest applicant's specific combination. The office has actually identified a long-felt need in the art that was not met until applicants taught this combination. The office now argues 3 additional references that merely discuss sill further recited elements somehow fill in all of the missing pieces. The office has

merely found pieces of applicant's combination in completely disparate references and then concocted an unsupportable "motivation" to have made this combination. There is nothing in the cited references that teach or suggest applicants' specific combination, so there cannot have been a reasonable expectation of success for this combination. See pages 12-13.

Applicant's traversal is acknowledged and is not found persuasive. In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The totality of the prior at the time the application was made teaches a nucleic acid construct for use in a method of stimulating comprising a nucleic acid construct comprising a nucleic acid sequence operatively linked to a promoter and using a cell-specific promoter that is operative in antigen-presenting cells (see Krieg). Krieg further teaches simultaneously administering an antigen with the nucleic acid construct or adding additional nucleotide sequences to the construct (column 3 and column 7). The only component not taught by Krieg is using either the CD80 promoter or the CD86 promoter, which are taught by Li or Zhang. Li teaches that the characterization of 5'-regulatory region (promoter region) of the human CD86 gene, which is expressed only in APCs. Zhang teaches that the CD80 promoter is expressed only in APCs. One of ordinary skill in the art would have been motivated to use the CD80 or CD86 promoter as the APC specific promoter in the construct of Krieg to elicit an immune response in a mammal because the CD80 and CD86 genes were known to one of ordinary skill in the art to specifically express in antigen presenting cells.

Furthermore, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, the examiner has taken only knowledge, which was within the level of ordinary skill at the time the claimed invention was made.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Thus, the traversal is not found persuasive for the reasons set forth above and the rejection for claims 1-5 and 11-19 remain under 103.

Claims 1-5 and 9-25 are rejected under 35 U.S.C 103(a) as being unpatentable over Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong in further view of Lai et al. (IDS, *DNA and Cell Biology*, Vol. 14(7), pp. 643-651, 1995).

The rejections of the base claims 1 and 14 under 35 U.S.C. 103(a) are applied here as indicated above, e.g., Krieg taken with Ellis in further view of either Li or Zhang, Krieg and Ellis in further view of either Li or Zhang taken with any Gurunathan, Wong, or Pulendran. Krieg taken with Ellis in further view of either Li or Zhang or Krieg and Ellis in further view of either

Li or Zhang taken with any Gurunathan, Wong, or Pulendran do not specifically teach using an immunogenic composition comprising core particle comprising a co-stimulatory promoter obtained from CD80 or CD86 gene operably linked to a polynucleotide sequence encoding at least one antigen in combination with at least one cytokine selected from the group consisting of CD40L, TRANCE, or Flt-3L in a method taught by Krieg.

However, at the time the invention was made, Lai teaches that a technique called biolistic transformation (biological ballistic system) microparticle injection, gene gun, or particle bombardment is rapid and specific for genetic immunization (abstract). The basic idea of this technique is that DNA or biological material coated onto heavy tungsten or gold particles is shot into target cells or animals (abstract). Lai expressed an antigen in a plasmid vector and introduced the vector into mice through two methods: (i) using a hand-held form of the biolistic system that can propel DNA-coated gold microprojectiles directly into the skin; (ii) using a conventional intramuscular injection of DNA into quadricep muscles of transfected mice (abstract). Both delivery systems induced humoral and cellular immunity in the experimental mice. In addition, Lai conducted trials in mice by injecting intramuscularly (i.m.) or gene gun administration a total of four injections at 2-week intervals or a total of three injections at intervals of 2 weeks, respectively (pg. 644-45); indicating a prime and booster administration of the immunogenic composition.

It would have been *prima facie* obvious for a person of ordinary skill in the art at the time the invention was made to coat the construct of the combined cited references Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong onto heavy tungsten or gold for transdermal delivery into a vertebrate subject using a gene gun as taught by Lai. One of

ordinary skill in the art would have been motivated to have employed the microparticle injection, gene gun, or particle bombardment wherein a metal particle is employed as a core carrier for delivering the immunogenic composition of the combined cited references because using a gene gun for genetic immunization saves time, money and labor, as taught by Lai.

Furthermore, it would have been obvious for a person of ordinary skill in the art to provide a prime and booster administrations of the immunogenic composition of the combine cited references to a vertebrate subject. One of ordinary skill in the art would have been motivated to have employed prime and booster administrations of the immunogenic composition in the subject because Lai teaches that the combination use of prime and booster administrations of an immunogenic composition would elicit a maximum immune response of a vertebrate subject to a targeted antigen.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant traverses the 103 rejection for the following reasons set forth above and: the addition of Lai to this unwieldy assembly of individual documents each discussing individual elements of applicant's recited combination simply fails to provide missing teaching or suggestion. See pages 13-15.

Applicant's traversal is acknowledged and is not found persuasive for the reasons set forth above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
12/26/02

DAVE T. NGUYEN
PRIMARY EXAMINER